Access DB# _____

SEARCH REQUEST FORM

Scientific and Technical Information Center

Requester's Full Name: David Lukton Examiner # : 71263 Date: 07-17-03

Art Unit: 1653 Phone Number 308-3213 Serial Number: 09/836,636

Mail Box and Bldg/Room Location: Mailbox: 9B01 ; Exr Rm: 9B05 Results Format Preferred (circle): PAPER DISK E-MAIL

If more than one search is submitted, please prioritize searches in order of need.

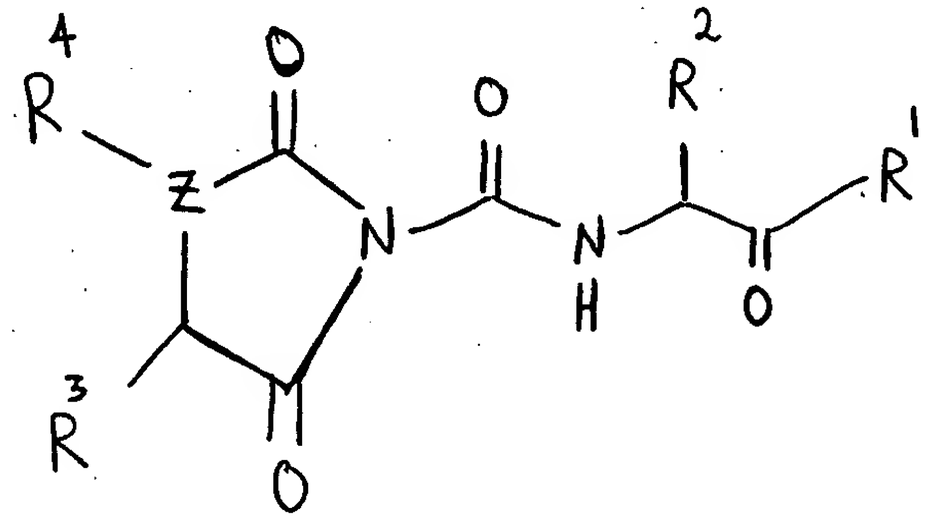
****

Title: Macrocyclic NS-3 serine protease inhibitors of Hepatitis C virus comprising alkyl and aryl alanine P2 moieties

Applicants: Venkatraman, Srikanth; Chen, Kevin X.; Arasappan, ashok; njoroge, f. George; girijavallabhan, viyyoor m.; ganguly, ashit k.; chan, tin-yau; mc kittrick, brian a.; yao, nanhua hugh; prongay, andrew j.; madison, vincent s.;

Earliest Priority Date: 4/19/00

* * * * * * *



Z is a nitrogen atom, or else –CH–

R1 = anything;
R2 = anything;
R3 = anything;
R4 = anything

Point of Contact
P. Sheppard
Telephone number: (703) 308-4499

****

STAFF USE ONLY

Searcher: _____

Searcher Phone #: _____

Searcher Location: _____

Date Searcher Picked Up: _____

Date Completed: 7/18/03

Searcher Prep & Review Time: _____

Clerical Prep Time: _____

Online Time: _____

Type of Search

NA Sequence (#)_____

AA Sequence (#)_____

Structure (#) _____

Bibliographic _____

Litigation _____

Fulltext _____

Patent Family _____

Other _____

Vendors and cost where applicable

STN _____

Dialog _____

Questel/Orbit _____

Dr.Link _____

Lexis/Nexis _____

Sequence Systems _____

WWW/Internet _____

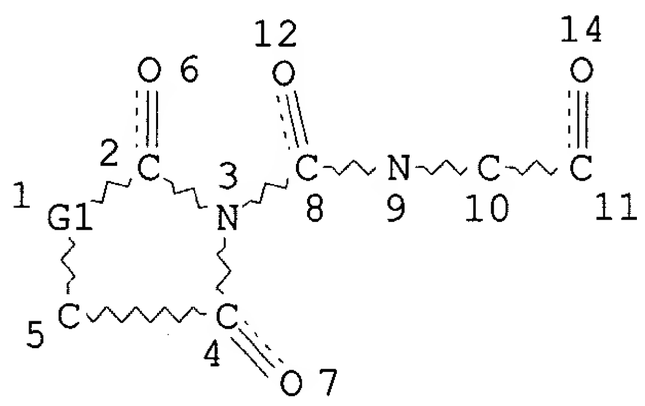
Other (specify) _____

PTO-1590 (8-01)

```
=> fil hcaplus
FILE 'HCAPLUS' ENTERED AT 18:47:10 ON 18 JUL 2003
USE IS SUBJECT TO THE TERMS OF YOUR STN CUSTOMER AGREEMENT.
PLEASE SEE "HELP USAGETERMS" FOR DETAILS.
COPYRIGHT (C) 2003 AMERICAN CHEMICAL SOCIETY (ACS)
```



```
FILE COVERS 1907 - 18 Jul 2003  VOL 139 ISS 4
FILE LAST UPDATED: 17 Jul 2003  (20030717/ED)

 This file contains CAS Registry Numbers for easy and accurate
 substance identification.

=>
=>

=> d stat que
L73                 STR
```



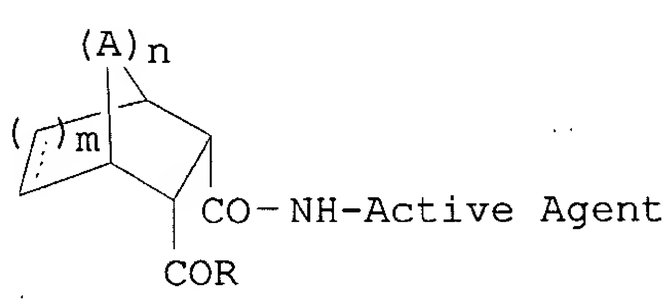

```
VAR G1=N/CH
NODE ATTRIBUTES:
DEFAULT MLEVEL IS ATOM
DEFAULT ECLEVEL IS LIMITED

GRAPH ATTRIBUTES:
RING(S) ARE ISOLATED OR EMBEDDED
NUMBER OF NODES IS  13

STEREO ATTRIBUTES: NONE
L79             6 SEA FILE=REGISTRY SSS FUL L73
L80             4 SEA FILE=HCAPLUS ABB=ON  PLU=ON  L79


=>
=>

=> d ibib abs hitrn 180 1-4

L80  ANSWER 1 OF 4  HCAPLUS  COPYRIGHT 2003 ACS
ACCESSION NUMBER:         1999:130413  HCAPLUS
DOCUMENT NUMBER:          130:182295
TITLE:                    Preparation of acid-cleavable bicyclic, nonaromatic
```

linker agents

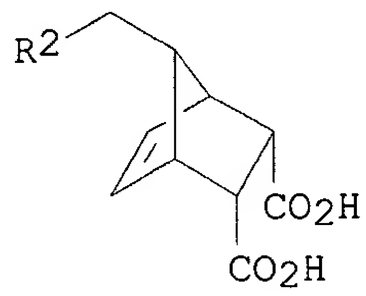
INVENTOR(S): Hadley, Stephen
PATENT ASSIGNEE(S): NeoRx Corporation, USA
SOURCE: U.S., 21 pp., Cont. of U.S. Ser. No. 589,579, abandoned.
CODEN: USXXAM
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 5874549	A	19990223	US 1993-118578	19930909
PRIORITY APPLN. INFO.:			US 1990-589579	19900928

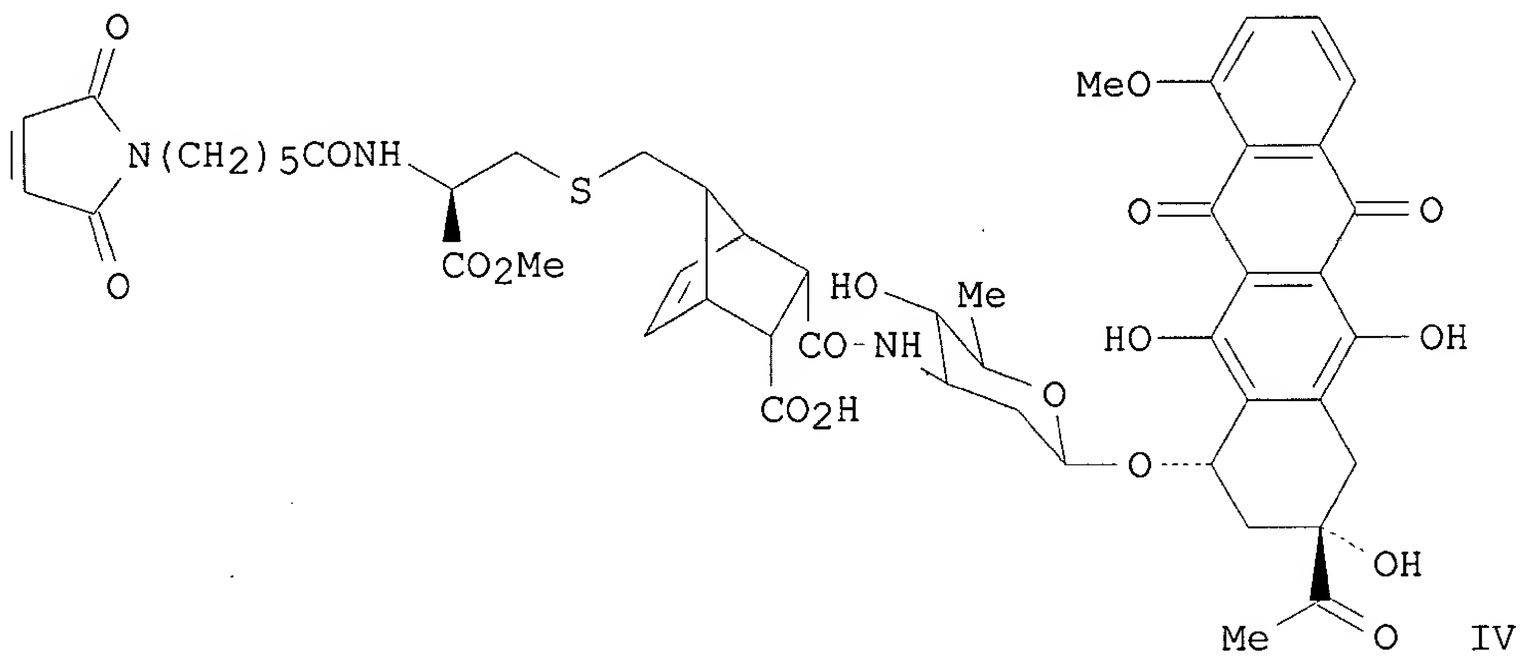
OTHER SOURCE(S): MARPAT 130:182295
GI



I



II



IV

AB A bicyclic, non-arom. hydrocarbon compd. I [A = CH2, n = 1-3; A = O, S, N-C1-6 alkyl, n = 1; m = 1, 2; R = H, OR1, SR1; R1 = ester moiety; Active agent = amino group-contg. therapeutic or diagnostic agent], acid-cleavably links an amide-contg. active agent to a targeting agent, which is linked by a linker arm to the bicyclic skeleton. Thus, alc. II (R2 = OH) (prepd. by sapon. and hydrogenolysis of the corresponding benzyl ether anhydride) was converted into mesylate II (R2 = MeSO3) and reacted with Boc-Cys-OMe to give sulfide II [R2 = (R)-BocNHCH(CO2Me)CH2S] (III). Acidic deprotection of III, followed by condensation with 6-maleimidocaproyl chloride, anhydride formation with DCC, and condensation with daunomycin gave drug conjugate IV.

IT **220495-15-8P 220495-16-9P 220495-22-7P**
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(prepn. of acid-cleavable bicyclic, nonarom. linker agents)

REFERENCE COUNT: 10 THERE ARE 10 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

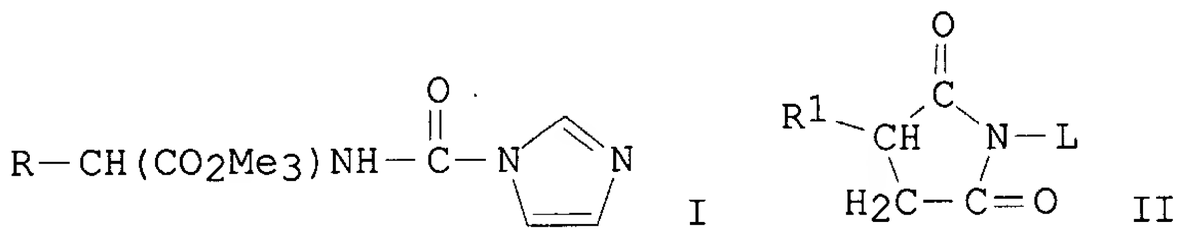
L80 ANSWER 2 OF 4 HCAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1991:20165 HCAPLUS
DOCUMENT NUMBER: 114:20165
TITLE: Amino acid azolides and other isocyanate-forming compounds as leukocyte elastase inhibitors
INVENTOR(S): Groutas, William C.
PATENT ASSIGNEE(S): Wichita State University, USA
SOURCE: U.S., 9 pp. Cont.-in-part of U.S. Ser. No. 756,252, abandoned.
CODEN: USXXAM
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 4929736	A	19900529	US 1987-117531	19871106
JP 62265221	A2	19871118	JP 1986-168235	19860718

PRIORITY APPLN. INFO.:

US	1985-756252	19850718
CA	1986-514030	19860717
JP	1986-168235	19860718

OTHER SOURCE(S): MARPAT 114:20165
GI



AB Isocyanate-forming compds. such as amino acid azolides (I; R = isoPr, Pr, Bu, isoBu, isoamyl) and substituted succinimides (II; R1 = alkyl or aryl, L = OSO2R) act as specific inhibitors of leukocyte elastase are described. These compds. are activated by the enzyme with the formation of an isocyanate that reacts with the serine at the active site. These compds. are useful in the treatment of emphysema. L-N-(imidazol-1-ylcarbonyl) norvaline Me ester (III) was prepd. by the reaction of equimolar masses of imidazole and L-norvaline Me ester isocyanate in anhyd. ether under N with 96% yield. Inhibition tests on elastase showed it to be an effective inhibitor of human leukocyte elastase but less effective against porcine pancreatic elastase (k3/Ki = 500 and 6.3 M-1 s-1 resp.). Tests conducted in vivo on elastase inhibition by III using induction of emphysematous lesions in mouse lung by instillation of porcine pancreatic elastase as a model were conducted. Preliminary expts. showed that III was not toxic when applied intratracheally. Simutaneous instillation of elastase and III prevented the formation of lesions for up to 10 days. Addn. of elastase after instillation of III showed that the inhibitor was unstable in vivo. If elastase was added >1 h after administration of III then there was no inhibition of lesion formation.

IT **131187-31-0P**
RL: PREP (Preparation)
(prepn. of, as elastase inhibitors, treatment of emphysema in relation to)

L80 ANSWER 3 OF 4 HCAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1989:496676 HCAPLUS

DOCUMENT NUMBER: 111:96676
TITLE: A method of preparing monosubstituted ureas as pharmaceutical and agrochemical intermediates
INVENTOR(S): Henklein, Peter; Bergemann, Dagmar; Heyne, Hans Ulrich; Halatsch, Wolf Rainer
PATENT ASSIGNEE(S): Akademie der Wissenschaften der DDR, Ger. Dem. Rep.
SOURCE: Ger. (East), 5 pp.
CODEN: GEXXA8
DOCUMENT TYPE: Patent
LANGUAGE: German
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

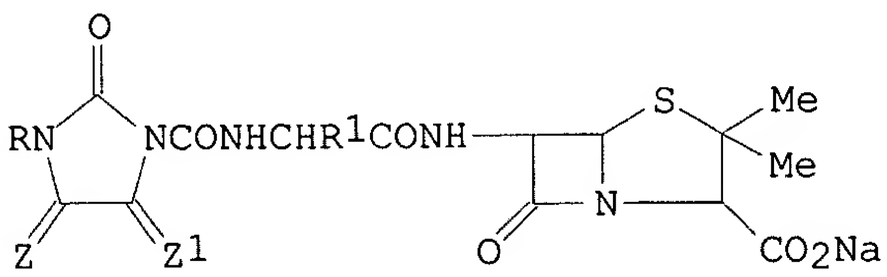
PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
DD 261781	A1	19881109	DD 1987-304600	19870703

PRIORITY APPLN. INFO.: DD 1987-304600 19870703
OTHER SOURCE(S): CASREACT 111:96676; MARPAT 111:96676
GI For diagram(s), see printed CA Issue.
AB RNHCONH2 [I; R = alkoxycarbonylalkyl, heteroaryl, (un)substituted alkyl, carboxyalkyl, aryl] were prepd. as pharmaceutical and agrochem. intermediates by room temp. ammonolysis of esters RNHCO2Q with aq. or gaseous NH3. PhCH2CH(NH2)CO2Et was stirred 30 min at 5.degree. and 30 min at room temp. with equimolar amt. of ClCO2Q in 40 mL CH2Cl2 to give crude PhCH2CH(CO2Et)NHCO2Q, which was dissolved in EtOAc and dry NH3 was bubbled through the stirred soln. to give 85% I [R = CH(CO2Et)CH2Ph]..
IT **121955-63-3P**
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(prepn. and ammonolysis of)

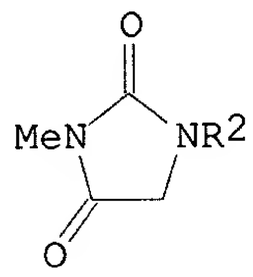
L80 ANSWER 4 OF 4 HCAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1979:23040 HCAPLUS
DOCUMENT NUMBER: 90:23040
TITLE: D-.alpha.-(2,4-Dioxo-1(or 3)-imidazolidinylcarbonylamino)benzylpenicillins
INVENTOR(S): Shibuya, Chisei; Ishii, Kunihiko; Ito, Hirataka
PATENT ASSIGNEE(S): Asahi Chemical Industry Co., Ltd., Japan
SOURCE: Jpn. Kokai Tokkyo Koho, 16 pp.
CODEN: JKXXAF
DOCUMENT TYPE: Patent
LANGUAGE: Japanese
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
JP 53077083	A2	19780708	JP 1976-150369	19761216

PRIORITY APPLN. INFO.: JP 1976-150369 19761216
GI



I



II

AB Five antibacterial penicillins I (R = Me, Ac, Ph; R1 = Ph, p-hydroxyphenyl; Z or Z1 = O and the other = H2) or their esters were

prepd. by acylating ampicillin, amoxicillin, 6-aminopenicillinac acid, or their esters. Thus, 0.9 g II (R2 = H) heated with 1.7 g bis(trimethylsilyl)acetamide in MeCN, evapd. in vacuo, and stirred with 0.8 g COCl2 in dioxane gave 1.3 g II (R2 = COCl), which (1.2 g) was added to 2.0 g ampicillin in 80% aq. THF at 0.degree. while adjusting the pH at 7.5-8.0 with Et3N and the product treated with Na 2-ethylhexanoate to give 1.9 g I (R = Me, R1 = Ph, Z = O, Z1 = H2). Its pivaloyloxymethyl ester was prepd. from corresponding ampicillin ester.

IT **68471-48-7P**
RL: SPN (Synthetic preparation); PREP (Preparation)
(prepn. of)

=>
=>
=> fil reg
FILE 'REGISTRY' ENTERED AT 18:47:22 ON 18 JUL 2003
USE IS SUBJECT TO THE TERMS OF YOUR STN CUSTOMER AGREEMENT.
PLEASE SEE "HELP USAGETERMS" FOR DETAILS.

Property values tagged with IC are from the ZIC/VINITI data file provided by InfoChem.

STRUCTURE FILE UPDATES: 17 JUL 2003 HIGHEST RN 550297-38-6
DICTIONARY FILE UPDATES: 17 JUL 2003 HIGHEST RN 550297-38-6

TSCA INFORMATION NOW CURRENT THROUGH JANUARY 6, 2003

Please note that search-term pricing does apply when conducting SmartSELECT searches.

Crossover limits have been increased. See HELP CROSSOVER for details.

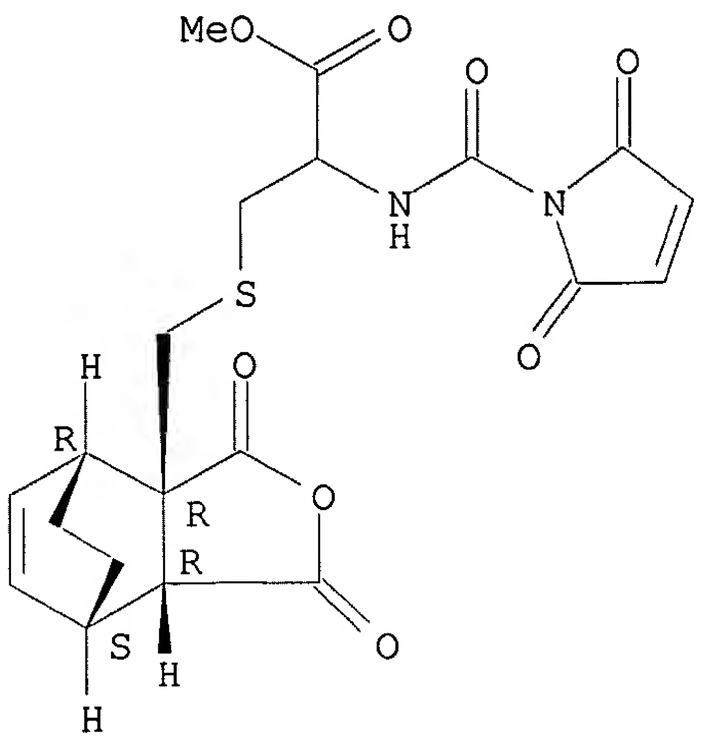
Experimental and calculated property data are now available. See HELP PROPERTIES for more information. See STNote 27, Searching Properties in the CAS Registry File, for complete details:
http://www.cas.org/ONLINE/STN/STNOTES/stnotes27.pdf

=>
=>

=> d ide can l79 1-6

L79 ANSWER 1 OF 6 REGISTRY COPYRIGHT 2003 ACS
RN 220495-22-7 REGISTRY
CN Cysteine, N-[(2,5-dihydro-2,5-dioxó-1H-pyrrol-1-yl)carbonyl]-S-[[(3aR,4R,7S,7aR)-1,4,7,7a-tetrahydro-1,3-dioxo-4,7-ethanoisobenzofuran-3a(3H)-yl]methyl]-, methyl ester, rel- (9CI) (CA INDEX NAME)
FS STEREOSEARCH
MF C20 H20 N2 O8 S
SR CA
LC STN Files: CA, CAPLUS, TOXCENTER, USPATFULL

Relative stereochemistry.

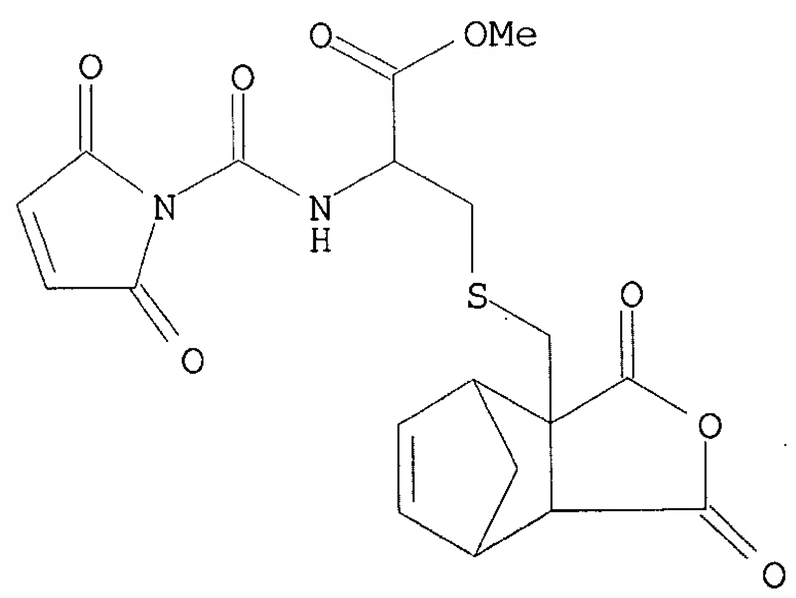


PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

1 REFERENCES IN FILE CA (1957 TO DATE)
1 REFERENCES IN FILE CAPLUS (1957 TO DATE)

REFERENCE 1: 130:182295

L79 ANSWER 2 OF 6 REGISTRY COPYRIGHT 2003 ACS
RN 220495-16-9 REGISTRY
CN L-Cysteine, N-[(2,5-dihydro-2,5-dioxo-1H-pyrrol-1-yl)carbonyl]-S-[[(3a.alpha.,4.alpha.,7.alpha.,7a.alpha.)-1,4,7,7a-tetrahydro-1,3-dioxo-4,7-methanoisobenzofuran-3a(3H)-yl]methyl]-, methyl ester (9CI) (CA INDEX NAME)
MF C19 H18 N2 O8 S
SR CA
LC STN Files: CA, CAPLUS, TOXCENTER, USPATFULL



PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

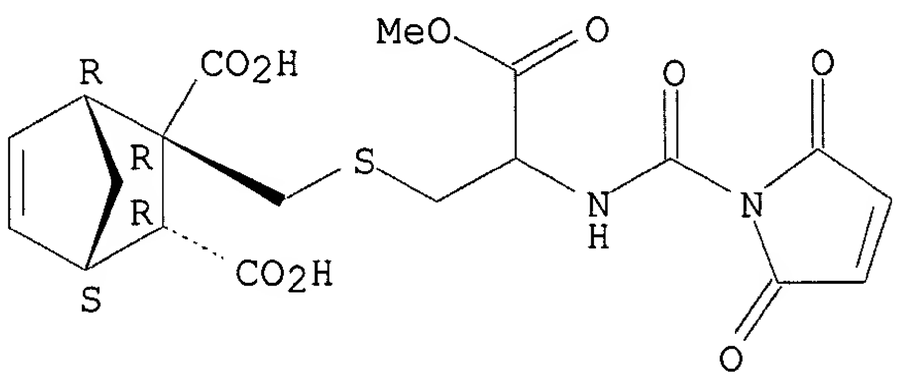
1 REFERENCES IN FILE CA (1957 TO DATE)
1 REFERENCES IN FILE CAPLUS (1957 TO DATE)

REFERENCE 1: 130:182295

L79 ANSWER 3 OF 6 REGISTRY COPYRIGHT 2003 ACS

RN 220495-15-8 REGISTRY
CN Bicyclo[2.2.1]hept-5-ene-2,3-dicarboxylic acid, 2-[[[2-[[(2,5-dihydro-2,5-dioxo-1H-pyrrol-1-yl)carbonyl]amino]-3-methoxy-3-oxopropyl]thio]methyl]-, (1R,2R,3R,4S)-rel- (9CI) (CA INDEX NAME)
FS STEREOSEARCH
MF C19 H20 N2 O9 S
SR CA
LC STN Files: CA, CAPLUS, TOXCENTER, USPATFULL

Relative stereochemistry.



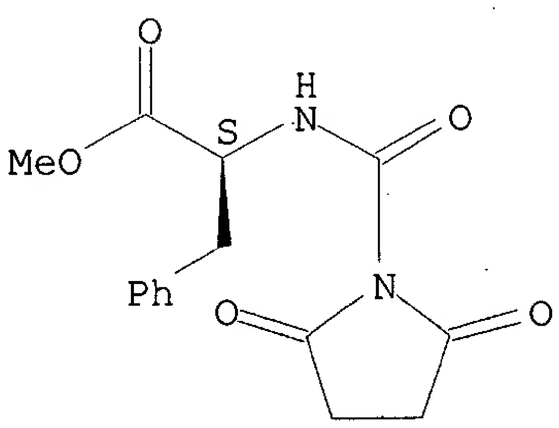
PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

1 REFERENCES IN FILE CA (1957 TO DATE)
1 REFERENCES IN FILE CAPLUS (1957 TO DATE)

REFERENCE 1: 130:182295

L79 ANSWER 4 OF 6 REGISTRY COPYRIGHT 2003 ACS
RN 131187-31-0 REGISTRY
CN L-Phenylalanine, N-[(2,5-dioxo-1-pyrrolidinyl)carbonyl]-, methyl ester (9CI) (CA INDEX NAME)
FS STEREOSEARCH
MF C15 H16 N2 O5
SR CA
LC STN Files: CA, CAPLUS, TOXCENTER, USPATFULL

Absolute stereochemistry.



PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

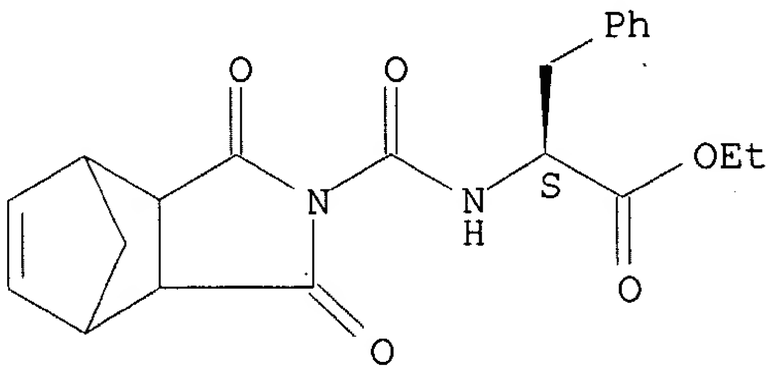
1 REFERENCES IN FILE CA (1957 TO DATE)
1 REFERENCES IN FILE CAPLUS (1957 TO DATE)

REFERENCE 1: 114:20165

L79 ANSWER 5 OF 6 REGISTRY COPYRIGHT 2003 ACS
RN 121955-63-3 REGISTRY

CN L-Phenylalanine, N-[(1,3,3a,4,7,7a-hexahydro-1,3-dioxo-4,7-methano-2H-isoindol-2-yl)carbonyl]-, ethyl ester (9CI) (CA INDEX NAME)
OTHER CA INDEX NAMES:
CN 4,7-Methano-2H-isoindole, L-phenylalanine deriv.
FS STEREOSEARCH
MF C21 H22 N2 O5
SR CA
LC STN Files: CA, CAPLUS

Absolute stereochemistry.



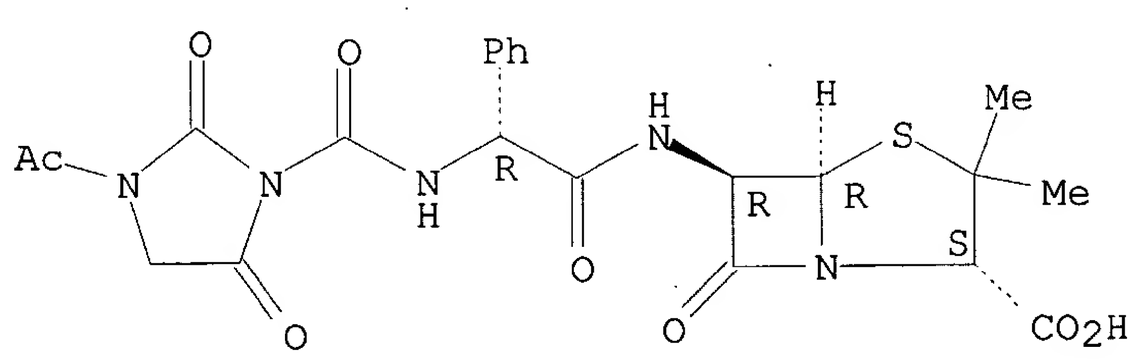
PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

1 REFERENCES IN FILE CA (1957 TO DATE)
1 REFERENCES IN FILE CAPLUS (1957 TO DATE)

REFERENCE 1: 111:96676

L79 ANSWER 6 OF 6 REGISTRY COPYRIGHT 2003 ACS
RN 68471-48-7 REGISTRY
CN 4-Thia-1-azabicyclo[3.2.0]heptane-2-carboxylic acid, 6-[[[[(3-acetyl-2,5-dioxo-1-imidazolidinyl)carbonyl]amino]phenylacetyl]amino]-3,3-dimethyl-7-oxo-, monosodium salt, [2S-[2.alpha.,5.alpha.,6.beta.(S*)]]- (9CI) (CA INDEX NAME)
FS STEREOSEARCH
MF C22 H23 N5 O8 S . Na
LC STN Files: CA, CAPLUS, TOXCENTER

Absolute stereochemistry.



● Na

1 REFERENCES IN FILE CA (1957 TO DATE)
1 REFERENCES IN FILE CAPLUS (1957 TO DATE)

REFERENCE 1: 90:23040